Primary immunodeficiencies may reveal potential infectious diseases associated with immune-targeting mAb treatments

László Maródi, MD, PhD,[a] and Jean-Laurent Casanova, MD, PhD[b,c] *Debrecen, Hungary, New York, NY, and Paris, France*

mAbs directed against immunologic molecules have emerged as a new class of drugs for treating patients with various immunologic conditions. However, mAb-based treatments may confer a predisposition to various infections. The authors argue that infections in individuals treated with mAbs directed against molecules of the immune system may display some similarities to those in patients with primary immunodeficiency of the corresponding mAb target. A comprehensive dissection of the tremendously diverse human primary immunodeficiencies and the careful description of their clinical features in different populations living in diverse environments thus represents an original, neglected, but promising approach to assessing the potential risk of infection associated with therapeutic mAbs, or with any therapeutic compound inhibiting a specific immunologic molecule. (J Allergy Clin Immunol 2010;126:910-7.)

Key words: *Primary immunodeficiency diseases, monoclonal antibody therapy, infections*

Abbreviations used

APS-1:	Autoimmune polyendocrine syndrome type 1
BAFF:	B-cell–activating factor
BAFF-R:	B-cell–activating factor receptor
HIES:	Hyper-IgE syndrome
HSE:	Herpes simplex virus encephalitis
HSV1:	Herpes simplex virus 1
IFN-γR:	IFN-γ receptor
IκBα:	Inhibitor of NF-κB-α
IL-1R:	IL-1 receptor
IL-12Rβ1:	IL-12 receptor β1
IRAK:	IL-1 receptor–associated kinase
JAK:	Janus-associated kinase
MS:	Multiple sclerosis
MSMD:	Mendelian susceptibility to mycobacterial disease
MyD88:	Myeloid differentiation factor 88
NEMO:	Nuclear factor-κB essential modulator
NF-κB:	Nuclear factor-κB
NTM:	Nontuberculous mycobacteria
OKT3:	Murine monoclonal antihuman CD3 antibody
PID:	Primary immunodeficiency
PML:	Progressive multifocal leukoencephalopathy
RA:	Rheumatoid arthritis
STAT:	Signal transducer and activator of transcription
T:	Transitional
TLR:	Toll-like receptor
VLA4:	Very late antigen 4

Many therapeutic mAbs target molecules involved in innate and adaptive immune responses.[1-3] They are used to treat patients with various immunologic conditions, including inflammatory and autoimmune diseases and hematologic malignancies. However, inhibiting the production or blocking the function of these targeted molecules may create an immunodeficiency, exposing the patient to a risk of infectious adverse events.[3-6] This risk is particularly great when the cell subsets carrying the targeted molecules are depleted.[6] We argue here that primary immunodeficiencies (PIDs) may be predictors of adverse effects of mAbs, including infectious diseases in particular.

Primary immunodeficiencies are inborn errors of immunity, typically inherited as monogenic traits.[2] Over the past decade, advances in research on PIDs have shed unexpected light on the basic mechanisms of the development and function of the immune system. The genetic defects that cause PIDs can affect the expression and function of proteins involved in various biological processes, such as immune development, effector-cell functions, signaling cascades, and the maintenance of immune homeostasis.[1,2] The number of identified PID-causing genes is rapidly increasing because of both the investigation of new phenotypes and the genetic dissection of well known phenotypes.[7]

It has been clearly demonstrated that autoimmunity to certain molecules precisely matches the clinical phenotype of inborn errors of the corresponding gene product or a closely related gene product. For example, pulmonary alveolar proteinosis caused by autoantibodies against GM-CSF mimics GM-CSF receptor deficiency.[8,9] Similarly, mycobacterial infections caused by autoantibodies against IFN-γ mimic IFN-γ receptor (IFN-γR) deficiency and IL-12p40 and IL-12 receptor β1 (IL-12Rβ1) deficiencies, in which IFN-γ induction is impaired.[10-13] Similarly, chronic mucocutaneous candidiasis has been found in patients lacking IL-17–producing T cells because of mutations in signal transducer and activator of transcription (STAT)–3,[14] patients with autoantibodies against IL-17 cytokines, and patients with autoimmune polyendocrine syndrome type 1 (APS-1) caused by mutations in the autoimmune regulator gene (*AIRE*).[15,16] If autoimmune

From [a]the Department of Infectious and Pediatric Immunology, University of Debrecen Medical and Health Science Center; [b]the Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, Rockefeller University Hospital, Rockefeller University, New York; and [c]Necker Branch, Paris Descartes University—INSERM U550, Necker Medical School, Paris.

Supported by TÁMOP grants (4.2.2-08/1/2008-0015 and 4.2.1/B-09/1/KONV-2010-0007) to L.M.

Disclosure of potential conflict of interest: The authors have declared that they have no conflict of interest.

Received for publication May 17, 2010; revised July 16, 2010; accepted for publication August 6, 2010.

Reprint requests: László Maródi, MD, PhD, Department of Infectious and Pediatric Immunology, University of Debrecen Medical and Health Science Center, Nagyerdei krt 98, 4032 Debrecen, Hungary. E-mail: lmarodi@dote.hu.

0091-6749/$36.00

doi:10.1016/j.jaci.2010.08.009

conditions involving the production of antibodies against immunologic components are similar to diseases caused by inborn errors of immune-associated genes, then there is every reason to believe that therapeutic mAbs may mimic these and other PIDs. Thus, the prolonged use of any mAb may result in a clinical syndrome resembling that of the corresponding (mutation in the target gene) or a related (mutation in a gene encoding a molecule closely related to the target) PID. This is clearly exemplified by infections occurring in patients on mAb treatment directed against CD20.[4,6]

However, there are important differences to consider when comparing patients with PID with those treated with mAbs. First, patients with PID have congenital defects—inborn errors of immunity—leading to immunodeficiency (and susceptibility to infection) from birth onward, whereas patients treated with mAbs are typically adults or, more rarely, children, with a fully competent immune system before mAb therapy. Second, the defects in PIDs may affect all cells and are typically complete, whereas the impact of mAbs may be restricted to certain cells and tissues and may not abolish the function of the molecule targeted. This situation is more reminiscent of the consequences of hypomorphic mutations, which typically cause mild variants of classic PIDs. Third, patients with PID usually display defects of multiple immunologic pathways, whereas mAb treatment targets a single pathway, making mechanistic extrapolation from PID phenotypes to mAb treatment difficult in some situations. For these reasons, the clinical outcome and phenotypic expression of many PIDs are likely to be more severe than observed in mAb-treated patients. Finally, there are a number of confounding factors (disease stage, immune status, duration of treatment, concomitant medication, age, ethnicity, endogenous levels of infectious agents, environmental exposure to infectious agents, and so forth) that may be unique to patients treated with mAbs or different between mAb-treated patients and those with PIDs. Despite these potential limitations, we believe that PIDs may be useful for identifying potential infectious hazards in patients treated with mAbs, and that important associations can be established to guide clinicians as concerns the pathogens to be monitored in mAb-treated patients or in clinical studies.

ANTIBODY THERAPY TARGETING LYMPHOCYTES

mAbs against CD20

The first connection between PIDs and mAb treatment was provided by B-cell–targeted mAb therapy. CD20 is a lineage-specific marker expressed by most mature B cells and involved in B-cell activation.[17] CD20-specific mAbs have been approved for the treatment of B-cell tumors and various B-cell–dependent autoimmune and inflammatory disorders, such as SLE and rheumatoid arthritis (RA).[4,17] They have also recently been shown to be effective in patients with refractory, severe, chronic Henoch-Schönlein purpura.[18] Several mechanisms, including antibody-dependent cellular cytotoxicity, complement-mediated lysis, and cell apoptosis, contribute to the robust B-cell depletion induced by treatment with antibodies against CD20.[17,19] However, one undesirable consequence of this treatment is that patients develop prolonged B-cell depletion resulting in antibody deficiency and potential infectious complications.[19,20] This clinical effect of B-cell depletion reaches a plateau after 12 to 16 weeks, and the number of circulating B cells remains low for 6 to 12 months.[17,21,22] Adjuvant rituximab therapy was associated with a significantly higher incidence of hypogammaglobulinemia between 12 and 24 months after autologous bone marrow transplantation.[20] Data from 356 hemato-oncology patients treated with anti-CD20 mAb showed an overall incidence rate of 30% for various infections and a mortality rate of 2%.[6,23] Antibody-mediated immunosuppression is unlikely to be solely responsible for infections, because this comparison was made in patients that already had an increased risk of infection. Thus, PIDs identify potential infectious hazards in mAb-treated patients.

The frequency of bacterial infections in patients treated with CD20-specific antibodies is particularly high when the interval between mAb injections is short or a high dose of mAb is injected.[24,25] Severe enteroviral diseases, which are typically seen in agammaglobulinemic patients,[1] have also been diagnosed in several patients treated with CD20-specific mAbs, and some of these patients were successfully treated with immunoglobulin replacement therapy.[26-30] Enteroviral diseases have not been diagnosed in patients treated with other mAbs. These observations highlight the importance of both the close monitoring of infectious diseases and the administration of regular infusions of IgG preparations to patients treated with anti-CD20 antibodies.

Rituximab was initially developed for the treatment of non-Hodgkin lymphoma and has subsequently been approved as a B-cell–directed therapy for RA; it is also increasingly used off-label for the treatment of patients with various autoimmune diseases.[17] Ocrelizumab, a humanized anti-CD20 antibody investigated in a phase II study for the treatment of RA, is much less antigenic than rituximab, a major advantage in this context. In addition to anti-CD20 antibodies, a number of other B-cell–directed therapies, such as anti-CD22 antibody (epratuzumab),[31] decoy receptor, the transmembrane activator and calcium modulating ligand interactor–immunoglobulin fusion protein (atacicept),[32] and anti—B-cell–activating factor (BAFF), have been tested in several autoimmune diseases.

mAbs against BAFF

BAFF–BAFF-receptor (BAFF-R) signaling plays a key role in the transition from immature transitional (T)–1 to T2 B cells and, therefore, in the generation of mature B cells in the spleen.[33] BAFF also plays a crucial role in the survival and maintenance of mature B cells.[33] Mice deficient in BAFF or BAFF-R have an almost complete lack of follicular and marginal zone B cells because T1 to T2 differentiation is blocked.[34,35] Biological activity was demonstrated for a new approach for blocking BAFF–BAFF-R signaling with a fully humanized anti-BAFF in early clinical trials for RA and SLE.[17] However, low immunoglobulin levels and B-cell counts were reported in this study. These adverse effects may have resulted in an increase in the risk of infection with bacterial and viral agents.

Murine monoclonal antihuman CD3 antibody treatment

Pan-T–cell—depleting agents with a broad spectrum of activity, including murine monoclonal antihuman CD3 antibody (OKT3), have been used for induction therapy in kidney and liver transplantation and for the treatment of steroid-resistant rejection episodes.[36] In a recent study, 8 of 43 recent renal transplant recipients (18.6%) developed severe bacterial infections and 1 patient (2.3%) was diagnosed with cytomegalovirus infection, indicating that OKT3 therapy may be associated with a potential

risk of infection in transplant patients.[36] The development of EBV-induced lymphoproliferative disorders in patients treated with OKT3 is well documented.[37,38] The T-cell depletion induced by OKT3 or another pan-T mAb may mimic PIDs involving functional T-cell deficiency or defects of T-cell development.[39]

mAbs against CD40 ligand (CD154)

Costimulatory signals, including the CD40 ligand (CD40L)/CD40 pathway, are critical for optimal T-cell activation and B-cell isotype switching.[40] CD40, a member of the TNF receptor superfamily, is expressed on resting B cells, macrophages, and dendritic cells, whereas CD154 is expressed only T cells, after antigen encounter and cell activation.[39,40] Several attempts have been made to block the CD154/CD40 pathway in rodents and nonhuman primates.[41-44] However, unanticipated thromboembolic complications led to the halting of clinical trials of anti-CD154 mAbs. The successful blockade of CD40L probably mimics X-linked hyper-IgM syndrome and may result in severe complications, such as infections with *Pneumocystis jirovecii* and other opportunistic pathogens, and neuroendocrine carcinoma.[45]

mAbs against CD52

Alemtuzumab is a humanized mAb directed against CD52, which is expressed by differentiated lymphocytes and monocytes.[17] Treatment with this mAb leads to a rapid and prolonged $CD4^+$ T-cell lymphopenia, resulting in cellular immunodeficiency and hypogammaglobulinemia. The possible use of this mAb for treating autoimmune diseases has been little explored because of its severe adverse effects, including the high risk of infection and cancer observed during initial clinical trials.[46]

Blockade of the T_H17 pathway

T_H17 cells have been proposed as a new subset of T_H cells, in addition to T_H1 and T_H2 cells.[47] These cells are thought to be involved in host defense against various microorganisms and fungi. T_H17 cells typically produce the IL-17A and IL-17F cytokines and have been implicated in the pathogenesis of autoimmune and inflammatory diseases, including RA. Recent studies in mice have suggested that IL-17 (and GM-CSF) blockade may suppress chronic destructive arthritis in animals no longer responsive to TNF-α antagonists.[48] However, such treatment may increase the risk of infection, because patients with the sporadic and autosomal-dominant forms of hyper-IgE syndrome (HIES), characterized by severe IL-17 depletion, are particularly susceptible to staphylococcal infections and candidiasis.[49] Furthermore, patients with APS-1 also display chronic mucocutaneous candidiasis.[50,51] We and others have recently shown that most patients with APS-1 have a high titer of neutralizing autoantibodies against IL-17A, IL-17F, and IL-22, in addition to antibodies against type 1 IFNs.[15,16] The clinical consequences of the production of autoantibodies against T_H17-associated cytokines may be similar to IL-17 depletion in HIES and may account for the high frequency of candidiasis in patients with APS-1.[50,51] Treatment with mAbs against IL-17 may therefore be a double-edged sword, and careful monitoring of side effects is required in patients receiving this biological treatment, paying particular attention to mucocutaneous infections caused by staphylococci and *Candida*.[52] It should be noted, however, that patients with HIES have immune defects other than impaired IL-17 production, such as impaired chemotaxis of neutrophils and low levels of IFN-γ production by T cells.

Antibodies targeting very late antigen 4

A therapeutic mAb has been developed against the α4 chain of the very late antigen 4 (VLA4) integrin molecule, which controls lymphocyte extravasation into the central nervous system.[53] In monotherapy, this mAb proved effective for the treatment of relapsing-remitting multiple sclerosis (MS), but it was withdrawn temporarily from the market because progressive multifocal leukoencephalopathy (PML) was detected in a number of patients treated with this mAb.[54] No PML had been reported in patients with MS before the introduction of this mAb, suggesting a causal relationship. PML is a fatal neurodegenerative disorder caused by infection with a polyomavirus (polyomavirus JC virus), resulting in damage to myelin-producing oligodendrocytes and demyelinization.[55] No primary α4 deficiency that might help to explain the possible relationship between VLA4 blockade and reactivation of polyomavirus JC virus in patients with MS has yet been identified.

THERAPEUTIC TARGETS OF THE INNATE IMMUNE SYSTEM

Most of the recently developed mAbs target components involved primarily in innate immunity. We therefore discuss how inborn errors of innate immunity may be mimicked by mAb treatment.

TNF inhibitors and genetic defects of TNF-mediated immunity

TNF is a key mediator of acute and chronic inflammatory responses (Fig 1). The past 10 years have seen TNF become a target for the treatment of various chronic inflammatory diseases in both adults and children.[56,57] TNF-blockade may be achieved with anti-TNF mAbs or soluble TNF receptors (Fig 1; Table I). However, patients treated with mAbs may become particularly susceptible to general infections and display the reactivation of previously acquired agents of disease, such as *Toxoplasma gondii*, *Mycobacterium tuberculosis*, and environmental nontuberculous mycobacteria (NTM) in particular.[4,5,58,59] In a large epidemiologic study of 5596 patients with RA treated with TNF-α antagonists, 37 infections occurred per 100 patient years versus 29 infections in the controls.[5] Intriguingly, the risk of tuberculosis reactivation posed by TNF-α antibodies appears to be greater than that in patients treated with soluble TNF receptors.[60]

No PID affecting the TNF-α cytokine or its receptor has yet been identified, but these infections were predicted by the mouse model, in which TNF-α is a key cytokine against *M tuberculosis*.[61] Moreover, these infections resemble those observed in PIDs affecting nuclear factor-κB (NF-κB) essential modulator (NEMO) and inhibitor of NF-κB-α (IκBα), in which cellular responses to TNF and other cytokines are impaired.[62] Mutations affecting NEMO and IκBα confer a predisposition to severe mycobacterial disease in addition to various bacterial, fungal, and viral diseases.[62] Infections in patients with NEMO and IκBα mutations result from a wide-ranging immunologic deficit, with the genetic defect also affecting pathways other than the TNF pathway. This impairment of other pathways, such as the

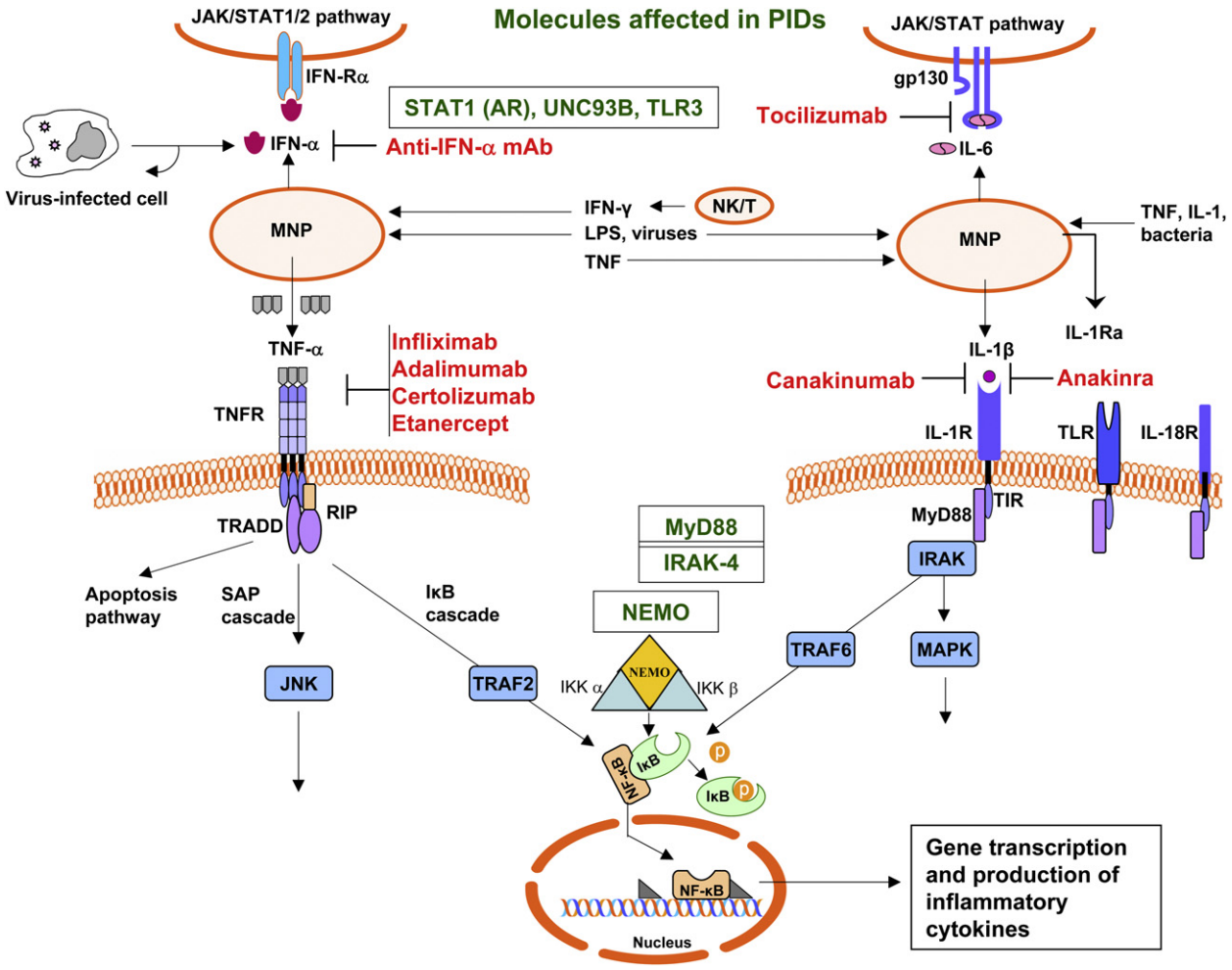

FIG 1. Interplay of innate immune responses and blocking of innate immunity by mAbs treatment. Mononuclear phagocytes *(MNPs)* secrete TNF-α after stimulation with IFN-γ, bacterial LPS, and viruses. TNF-α induces the secretion of proinflammatory cytokines, including IL-1β and IL-6, by MNPs *(right)*. TNF receptor initiates the inhibitor of NF-κB *(IκB)* cascade, which leads to the activation of gene transcription and the production of inflammatory cytokines *(bottom)*. Binding of ligands to the IL-1β receptor or the TLR *(TIR)* domain leads to binding of MyD88 and IRAK *(right)*. Next, IRAK-4 dissociates from the receptor-adapter complex and binds TNF receptor-associated factor *(TRAF)*–6, thereby activating the NF-κB pathway, resulting in gene transcription and the production of inflammatory mediators. MNPs also produce the natural antagonist IL-1Ra *(right)*. mAbs directed against cytokines or cytokine receptors are indicated in *red*, and the corresponding PIDs are shown in *green*. *AR,* Autosomal-recessive; *IKK,* inhibitor of κB kinase, *MAPK,* Mitogen-activated protein kinase; *NK,* natural killer; *RIP,* receptor interacting protein; *SAP,* stress-activated protein; *T,* T cell; *TRADD,* TNF-receptor-associated death domain.

induction of IL-12 by CD40, may also contribute to the development of mycobacterial disease in these patients (Figs 1 and 2).[63] Although these PIDs are not specifically associated with defects in TNF-α or its receptor, they may be useful for assessing the potential increase in the risk of infectious diseases associated with TNF-specific antibodies. The lower incidence of *Mycobacterium tuberculosis* infection in patients receiving anti-TNF treatment than in PID patients suggests that PID attacks more complex pathways than are affected in patients treated with TNF-specific mAbs.

IL-1 blockade and primary defects of the IL-1 receptor–associated kinase pathway

Human anti-IL-1β mAb has been approved for use in the treatment of cryopyrin-associated periodic syndrome and Muckle-Wells syndrome.[64] IL-1 can also be inhibited by treatment with anakinra, a soluble recombinant IL-1 receptor (IL-1R; Fig 1).[65] However, immunotherapy targeting IL-1β may be associated with a risk of adverse infectious events. These events may include invasive pyogenic infections, as observed in IL-1 receptor–associated kinase (IRAK)—4 and myeloid differentiation factor 88 (MyD88) deficiencies (Fig 1; Table I), both of which impair Toll-like receptor (TLR) and IL-1R pathways (including responses to IL-1, IL-18, and IL-33).[66,67] It is currently difficult to establish a direct link between anti–IL-β mAb treatment and IRAK4 or MydD88 deficiency because these deficiencies abolish signaling through multiple members of the IL-1R and TLR families. However, the discovery of patients with primary IL-1 or IL-1R deficiency would make it possible to address this issue and to assess the infectious risk associated

TABLE I. Immunologic targets and the therapeutic mAbs considered in this review and their corresponding PIDs

Target molecule	Target cell	Generic name (trade name)	Corresponding PIDs
CD20	B cells	Rituximab (MabThera)	X-linked and AR agammaglobulinemia
TNF-α	MNP	Infliximab (Remicade)	NF-κB essential modulator
		Adalimumab (Humira)	
		Certolizumab (Cimzia)	Inhibitor of NF-κB kinase-α
TNF-αR	MNP	Etanercept (Enbrel)	
IL-1β	MNP	Canakinumab (Ilaris)	IRAK4, MyD88
IL-1R	MNP	Anakinra (Kineret)	
IFN-α	All	NA	STAT1 (AR), TYK2, UNC-93B, and TLR3
IL-6 receptor	All	Tocilizumab (Actemra)	Not yet defined
IFN-γ	MNP	Fontolizumab (HuZAF)	IFN-γR1, IFN-γR2, and STAT1 (AD)
IL-12 p40	MNP	Ustekinumab (Stelara)	IL-12p40, IL-12Rβ1
VLA4	Lymphocytes	Natalizumab (Tysabri)	Not yet defined

AD, Autosomal-dominant; *AR,* autosomal-recessive; *MNP,* mononuclear phagocyte; *NA,* not applicable; *TYK2,* tyrosine kinase 2.

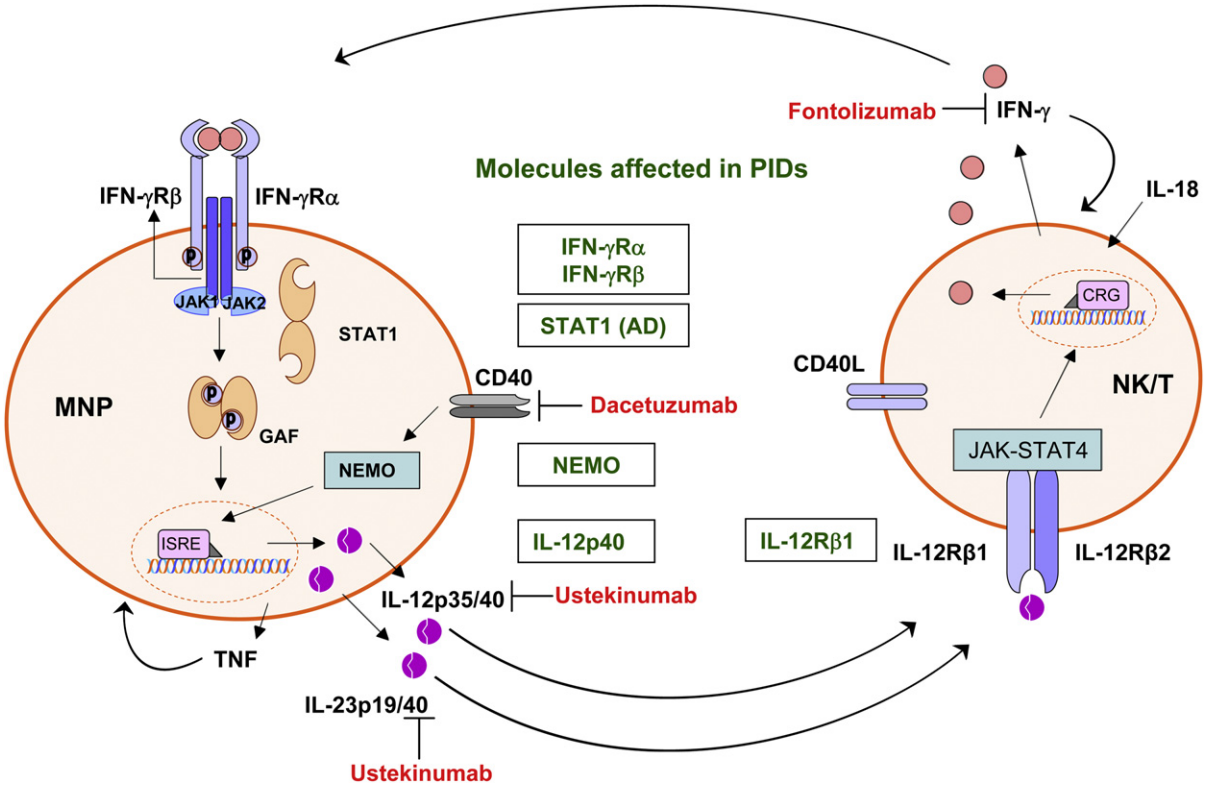

FIG 2. Schematic representation of primary deficiencies and mAbs targets of the IL-12–IL-23–IFN-γ circuit. Phagocytic uptake by mononuclear phagocytes *(MNPs)* is accompanied by the release of IL-12 and IL-23, which share the p40 component and bind to the same receptor. Receptor binding initiates signaling and stimulates the production of IFN-γ by natural killer/T cells. IFN-γ homodimers then bind to the IFN-γRα chain and initiate signaling through the IFN-γRβ associated with JAK1 and JAK2. Cross-phosphorylation generates docking sites for STAT1, which, after phosphorylation, forms active homodimers. Active STAT1 homodimers are translocated to the nucleus, where they promote the transcription of genes with IFN-stimulated response elements *(ISRE).* mAbs directed against cytokines or cytokine receptors are indicated in *red,* and the corresponding PIDs are shown in *green. AD,* Autosomal-dominant; *CRG,* cytokine responsive gene; *GAF,* gamma-interferon activation factor.

with treatment based on the use of mAbs targeting these molecules. This hypothesis is supported by the observation that the risk of infection with gram-positive bacteria is no higher than normal in patients treated for up to 5 years with canakinumab (Ilaris, Novartis, Cambridge, Mass). However, a recent meta-analysis of 4 clinical trials revealed that patients with RA treated with high doses of anakinra had a higher risk of severe infections, including pneumonia, osteomyelitis, and cellulitis.[68]

Antibody blockade of IL-6

The inflammatory cytokine IL-6 is produced by various cells in response to stimulation with TNF, IL-1, or bacteria.[69] Antibodies against human IL-6 or its receptor (tocilizumab) have recently been approved for use in the treatment of patients with RA and other inflammatory diseases.[70] No PIDs of IL-6 or its receptor have been described to date, but particularly high levels of IL-6–specific autoantibody production have been observed in a

patient with recurrent staphylococcal cellulitis and subcutaneous abscesses.[71] Monitoring for infectious complications, particularly those caused by staphylococci, is therefore probably worthwhile in patients on IL-6–blocking mAb treatment. The identification of patients with IL-6 and IL-6 receptor deficiencies is awaited to allow firm conclusions to be drawn.

Phenotypes of PIDs and possible adverse effects of anti-IFN type I antibodies

Type I IFNs (IFN-α/β) mediate early innate antiviral responses through binding to their receptor, which initiates the Janus-associated kinase (JAK)/STAT signaling pathway (Fig 1). Type I IFNs are overproduced in patients with SLE, and phase I trials are currently underway to evaluate the safety of IFN-α–specific mAb treatment for this autoimmune disease.[72,73] Careful monitoring of the adverse effects of these mAbs is important because PIDs affecting IFN responses are known to result in susceptibility to a broad range of viral infections, including herpes simplex virus 1 (HSV1) infection of the skin and central nervous system.[74,75]

Primary defects of the UNC93B-dependent and TLR3-dependent pathway have also been reported to impair immunity to primary infection with HSV1 and to predispose children to HSV1 encephalitis (HSE), the most common sporadic viral encephalitis in Western countries.[76,77] UNC93B is an endoplasmic reticulum protein involved in signaling through TLR3, TLR7, and TLR9.[78] Recent reports suggest that mutations in *UNC93B1* or *TLR3* may result in the impairment of IFN-α/β production after TLR3 stimulation.[76,77] There is no induction of any cytokine downstream from these receptors, but we know that the only symptomatic defect is a lack of IFN-α/β and IFN-λ induction because of the similar phenotype of STAT1-deficient patients (ie, those with HSE) who do not respond to these IFNs but do respond to other cytokines. IFN-α/β (or TLR3) blockade would therefore be expected to result in an increase in viral susceptibility, including HSE, particularly in patients who have not yet been infected with HSV1. The risk is probably lower in individuals previously infected with HSV-1 because the TLR3-IFN pathway appears to be important for immunity to primary but not latent HSV-1 infection in the central nervous system. This hypothesis is supported by the observation that STAT1-deficient patients are prone to HSE and do not respond to IFN-α/β, IFN-λ, IFN-γ, and IL-27. However, IFN-γR–deficient patients are not vulnerable to HSE. In addition, TLR3/UNC93B-deficient patients produce IL-27 normally but do not produce IFN-α/β and IFN-λ. There may be other viral risks, but these remain to be identified because we have identified only a few STAT1-deficient and TLR3/UNC93B-deficient patients to date.

Antibody therapy targeting the IL-12–IL-23–IFN-γ circuit

Mendelian susceptibility to mycobacterial disease (MSMD) is a group of innate genetic disorders characterized by susceptibility to infections caused by weakly virulent mycobacteria, such as BCG and NTM, in otherwise healthy individuals.[59,61,62] Mutations in genes involved in the IL-12–IL-23–IFN-γ circuit have been implicated in MSMD (Fig 2).[59] In addition, high-titer anti–IFN-γ antibodies have been identified as pathogenic factors in patients with severe NTM infections.[10-13] These observations not only reinforce the links between PIDs and autoimmunity but also reveal the value of "experiments of nature" for predicting the possible side effects of mAbs against IFN-γ, which were recently studied in patients with Crohn disease.[79] Although increased susceptibility to mycobacteria was not observed in a recent phase II clinical trial of this mAb, which found tolerability to be favorable, further studies to assess its safety are warranted.[79]

Novel biological strategies are being developed for treating patients with psoriasis because several cytokines, including IL-12 and IL-23, have been implicated in the pathogenesis of this chronic inflammatory skin disease. The short-term clinical efficacy of mAbs against the p40 subunit of IL-12 and IL-23 for the treatment of plaque psoriasis has been demonstrated (Fig 2).[80] The clinical presentation of patients with genetic IL-12p40 deficiency (and IL-12Rβ1 deficiency)[81,82] suggests that MSMD and *Salmonella* infection are possible complications of long-term treatment with antibodies against IL-12 p40 (or IL-12Rβ1). Other infectious diseases, more rare in patients with these PIDs, might also occur in those treated with such mAbs. Two young patients with inborn errors of the IL-12–IL-23–IFN-γ circuit and very unusual cancers, in terms of both age of onset and severity, have recently been reported,[83,84] suggesting that predisposition to cancer should be carefully monitored in patients receiving mAbs against IL-12p40, IL-12Rβ1, or IFN-γ.

In conclusion, PIDs may teach us about the potential adverse effects of mAbs, especially the increasingly recognized PIDs affecting innate immunity. Adverse effects of mAbs, infectious in particular, appear to be an increasingly recognized risk. By contrast, the infectious diseases associated with PIDs actually led to the discovery of PIDs. Although there is currently only modest evidence that PIDs may be seen as predictors of adverse infectious diseases in patients treated with mAbs, it seems both prudent and reasonable, in the patients' best interest, to consider that they may be so. This may apply to other treatments, such as small chemical inhibitors or intracellular molecules involved in immunity, such as IRAK4.[85,86] The existing evidence is consistent with this prediction, as discussed. Animal models may also be good predictors, as exemplified by TNF-deficient mice, which clearly predicted the mycobacterial disease documented in patients treated with TNF-specific mAbs. In any event, we merely aim to draw the attention of clinicians and practitioners, the pharmaceutical industry, and regulatory agencies to the potential contribution of the field of PIDs to the detection and management of potential infections in patients receiving therapeutic mAbs.

The treatment of immunologic diseases with mAbs has been made possible by advances in molecular engineering within the biotechnology and pharmaceutical industries. The agents developed are target-specific, and their mode of action is usually immunologically well defined, making it possible to anticipate potential side effects, such as specific infectious complications in patients receiving these mAbs. Conversely, unpredictable infectious adverse events may be so severe that they necessitate the temporary withdrawal of the mAb concerned, as was the case for mAbs against VLA4. Natalizumab (Tysabri, Biogen Idec, Weston, Mass) is now back on the market as a monotherapy. Other side effects may be foreseen by analyzing PIDs, which, like autoimmune syndromes in which antibodies against immune system molecules are produced, are "experiments of nature" providing useful insight. The risk of infectious complications may vary significantly, depending on the nature of the underlying disease against which biological agents are used and other concomitant treatment. The side effects of mAbs may also differ between populations, further

highlighting the need for the public and private sectors to work together in research and for physician education and research collaboration programs.[87-89] Such research should be funded by both public research organizations and pharmaceutical companies, given the increasing number of new therapeutic mAbs entering clinical trials. Research into rare PIDs, by improving our understanding and prediction of the infectious adverse effects of therapeutic mAbs, may have a considerable public health impact.

We thank Melinda Erdős for her help with artwork for this article.

REFERENCES

1. Maródi L, Notarangelo LD. Immunological and genetic bases of new primary immunodeficiencies. Nat Rev Immunol 2007;11:851-61.
2. Casanova JL, Abel L. Primary immunodeficiencies: a field in its infancy. Science 2007;317:617-9.
3. Maródi L, Casanova JL. Can primary immunodeficiencies help to provide insights into infectious risks of therapeutic antibodies? Nat Rev Immunol 2010;10:299-300.
4. Martin-Mola E, Balsa A. Infectious complications of biologic agents. Rheum Dis Clin N Am 2009;35:183-99.
5. Desai SB, Furst DE. Problems encountered during anti-tumor necrosis factor therapy. Best Pract Res Clin Rheumatol 2006;20:757-90.
6. Kimby E. Tolerability and safety of rituximab (MabThera). Cancer Treat Rev 2005;31:456-73.
7. Notarangelo LD, Casanova JL. Primary immunodeficiencies: increasing market share. Curr Opin Immunol 2009;21:461-5.
8. Suzuki T, Sakagami T, Rubin BK, Nogee LM, Wood RE, Zimmerman SL, et al. Familial pulmonary alveolar proteinosis caused by mutations in CSF2RA. J Exp Med 2008;205:2703-10.
9. Martinez-Moczygemba M, Martinez-Moczygemba M, Doan ML, Elidemir O, Fan LL, Cheung SW, et al. Pulmonary alveolar proteinosis caused by deletion of the GM-CSFRα gene in the X chromosome pseudoautosomal region. J Exp Med 2008;205:2711-6.
10. Patel SY, Ding L, Brown MR, Lantz L, Gay T, Cohen S, et al. Anti-IFN-γ autoantibodies in disseminated non-tuberculous mycobacterial infections. J Immunol 2005;175:4769-76.
11. Döffinger R, Helbert MR, Barcenas-Morales G, Yang K, Dupuis S, Ceron-Gutierrez L, et al. Autoantibodies to interferon-gamma in a patient with selective susceptibility to mycobacterial infection and organ-specific autoimmunity. Clin Infect Dis 2004;38:e10-4.
12. Kampmann B, Hemingway C, Stephens A, Davidson R, Goodsall A, Anderson S, et al. Acquired predisposition to mycobacterial disease due to autoantibodies to IFN-gamma. J Clin Invest 2005;115:2480-8.
13. Höflich C, Sabat R, Rosseau S, Temmesfeld B, Slevogt H, Döcke WD, et al. Naturally occurring anti-IFN-gamma autoantibody and severe infections with *Mycobacterium cheloneae* and *Burkholderia cocovenenans*. Blood 2003;103:673-5.
14. Minegishi Y, Saito M, Nagasawa M, Takada H, Hara T, Tsuchiya S, et al. Molecular explanation for the contradiction between systemic Th17 defect and localized bacterial infection in hyper-IgE syndrome. J Exp Med 2009;206:1291-301.
15. Puel A, Döffinger R, Natividad A, Chrabieh M, Barcenas-Morales G, Picard C, et al. Autoantibodies against IL-17A, IL-17F and IL-22 in patients with chronic mucocutaneous candidiasis and autoimmune polyendocrine syndrome type I. J Exp Med 2010;207:291-7.
16. Kisand K, Bøe Wolff AS, Podkrajsek KT, Tserel L, Link M, Kisand KV, et al. Chronic mucocutaneous candidiasis in APECED or thymoma patients correlates with autoimmunity to Th17-associated cytokines. J Exp Med 2010;207:299-308.
17. Dörner T, Radbruch A, Burmester GR. B-cell-directed therapies for autoimmune disease. Nat Rev Rheumatol 2009;5:433-41.
18. Donnithorne KJ, Atkinson TP, Hinze CH, Nogueira JB, Saeed SA, Askenazi DJ, et al. Rituximab therapy for severe refractory chronic Henoch-Schönlein purpura. J Pediatr 2009;155:136-9.
19. Ben-Bassat I, Shpilberg O, Polliack A, Raanani P. The late adverse events of rituximab therapy—rare but there. Leuk Lymphoma 2009;50:1083-95.
20. Shortt J, Spencer A. Adjuvant rituximab causes prolonged hypogammaglobulinaemia following autologous stem cell transplant for non-Hodgkin's lymphoma. Bone Marrow Transplant 2006;38:433-6.
21. Cohen SB, Emery P, Greenwald MW, Dougados M, Furie RA, Genovese MC, et al. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum 2006;54:2793-806.
22. Hauser SL, Waubant E, Arnold DL, Vollmer T, Antel J, Fox RJ, et al. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. N Engl J Med 2008;358:676-88.
23. Cornely OA, Ullmann AJ, Karthaus M. Opportunistic infections after treatment with monoclonal antibodies. Wien Med Wochenschr 2004;154:209-17.
24. Kanbayashi Y, Nomura K, Fujimoto Y, Yamashita M, Ohshiro M, Okamoto K, et al. Risk factors for infection in haematology patients treated with rituximab. Eur J Haematol 2009;82:26-30.
25. Katchamart W, Johnson S, Lin HJ, Phumethum V, Salliot C, Bombardier C. Predictors for remission in rheumatoid arthritis patients: a systematic review. Arthritis Care Res 2010;62:1128-43.
26. Kiani-Alikhan S, Skoulidis F, Barroso A, Nuovo G, Ushiro-Lumb I, Breuer J, et al. Enterovirus infection of neuronal cells post-rituximab. Br J Haematol 2009;146:333-5.
27. Ganjoo KN, Raman R, Sobel RA, Pinto HA. Opportunistic enteroviral meningoencephalitis: an unusual treatable complication of rituximab therapy. Leuk Lymphoma 2009;50:673-5.
28. Padate BP, Keidan J. Enteroviral meningoencephalitis in a patient with non-Hodgkin's lymphoma treated previously with rituximab. Clin Lab Haematol 2006;28:69-71.
29. Archimbaud C, Bailly JL, Chambon M, Tournilhac O, Travade P, Peigue-Lafeuille H. Molecular evidence of persistent echovirus 13 meningoencephalitis in a patient with relapsed lymphoma after an outbreak of meningitis in 2000. J Clin Microbiol 2003;41:4605-10.
30. Quartier P, Tournilhac O, Archimbaud C, Lazaro L, Chaleteix C, Millet P, et al. Enteroviral meningoencephalitis after anti-CD20 (rituximab) treatment. Clin Infect Dis 2003;36:e47-9.
31. Dörner T, Kaufmann J, Wegener WA, Teoh N, Goldenberg DM, Burmester GR. Initial clinical trial of epratuzumab (humanized anti-CD22 antibody) for immunotherapy of systemic lupus erythematosus. Arthritis Res Ther 2006;8:R74.
32. Dall'Era M, Chakravarty E, Wallace D, Genovese M, Weisman M, Kavanaugh A, et al. Reduced B lymphocyte and immunoglobulin levels after atacicept treatment in patients with systemic lupus erythematosus: results of a multicenter, phase Ib, double-blind, placebo-controlled, dose-escalating trial. Arthritis Rheum 2007;56:4142-50.
33. Rauch M, Tussiwand R, Bosco N, Roling AG. Crucial role for BAFF-BAFF-R signaling in the survival and maintenance of mature B cells. PloS One 2009;4:e5456.
34. Schiemann B, Gommerman JL, Vora K, Cachero TG, Shulga-Morskaya S, Dobles M, et al. An essential role for BAFF in the normal development of B cells through a BCMA-independent pathway. Science 2001;293:2111-4.
35. Sasaki Y, Casola S, Kutok JL, Rajewsky K, Schmidt-Supprian M. TNF family member B cell-activating factor (BAFF) receptor-dependent and -independent roles for BAFF in B cell physiology. J Immunol 2004;173:2245-52.
36. Sevmis S, Emiroglu R, Karakayali F, Yagmurdur MC, Dalgic A, Moray G, et al. OKT3 treatment for steroid-resistant acute rejection in kidney transplantation. Transplant Proc 2005;37:3016-8.
37. Barkholt L, Linde A, Falk KI. OKT3 and ganciclovir treatments are possibly related to the presence of Epstein-Barr virus in serum after liver transplantation. Transpl Int 2005;18:835-43.
38. Burra P, Buda A, Livi U, Rigotti P, Zanus G, Calabrese F, et al. Occurrence of post-transplant lymphoproliferative disorders among over thousand adult recipients: any role for hepatitis C infection? Eur J Gastroenterol Hepatol 2006;18:1065-70.
39. Geha RS, Notarangelo LD, Casanova JL, Chapel H, Conley ME, Fischer A, et al. Primary immunodeficiency diseases: an update from the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee. J Allergy Clin Immunol 2007;120:776-94.
40. Erdős M, Durandy A, Maródi L. Genetically-acquired class-switch recombination defects: the multi-faced hyper-IgM syndrome. Immunol Lett 2005;97:1-6.
41. Ford ML, Larsen CP. Translating costimulation blockade to the clinic: lessons learned from three pathways. Immunol Rev 2009;229:294-306.
42. Kirk AD, Burkly LC, Batty DS, Baumgartner RE, Berning JD, Buchanan K, et al. Treatment with humanized monoclonal antibody against CD154 prevents acute renal allograft rejection in nonhuman primates. Nat Med 1999;5:686-93.
43. Kenyon NS, Fernandez LA, Lehmann R, Masetti M, Ranuncoli A, Chatzipetrou M, et al. Long-term survival and function of intrahepatic islet allografts in baboons treated with humanized anti-CD154. Diabetes 1999;48:1473-81.
44. Parker DC, Greiner DL, Phillips NE, Appel MC, Steele AW, Durie FH, et al. Survival of mouse pancreatic islet allografts in recipients treated with allogeneic small lymphocytes and antibody to CD40 ligand. Proc Natl Acad Sci U S A 1995;92:9560-4.

45. Erdős M, Garami M, Rákóczi É, Zalatnai A, Steinbach D, Baumann U, et al. Neuroendocrine carcinoma associated with X-linked hyper-immunoglobulin M syndrome: report of four cases and review of the literature. Clin Immunol 2008; 129:455-61.
46. Coles AJ, Compston DA, Selmaj KW, Lake SL, Moran S, Margolin DH, et al. Alemtuzumab vs. interferon beta-1a in early multiple sclerosis. N Engl J Med 2008;359:1786-801.
47. Dong C. TH17 cells in development: an updated view of their molecular identity and genetic programming. Nat Rev Immunol 2008;8:337-48.
48. Plater-Zyberk C, Joosten LA, Helsen MM, Koenders MI, Baeuerle PA, van den Berg WB. Combined blockade of granulocyte-macrophage colony stimulating factor and interleukin 17 pathways potently suppresses chronic destructive arthritis in a tumor necrosis factor alpha-independent mouse model. Ann Rheum Dis 2009;68: 721-8.
49. Minegishi Y, Saito M, Tsuchiya S, Tsuge I, Takada H, Hara T, et al. Dominant-negative mutations in the DNA-binding domain of STAT3 cause hyper IgE syndrome. Nature 2007;448:1058-62.
50. Husebye ES, Perheentupa J, Rautemaa R, Kämpe O. Clinical manifestations and management of patients with autoimmune polyendocrine syndrome type I. J Intern Med 2009;265:514-29.
51. Tóth B, Wolff A, Halász Z, Tar A, Szüts P, Ilyés I, et al. Novel sequence variation of AIRE and detection of interferon-ω antibodies in early infancy. Clin Endocrinol 2010;72:641-7.
52. Netea MG, Maródi L. Innate immune mechanisms for recognition and uptake of *Candida* species. Trends Immunol 2010;31:346-53.
53. Carson KR, Focosi D, Major EO, Petrini M, Richey EA, West DP, et al. Monoclonal antibody-associated progressive multifocal leucoencephalopathy in patients treated with rituximab, natalizumab, and efalizumab: a review from the research on adverse drug events and reports (RADAR) project. Lancet 2009;10:816-24.
54. Major EO. Reemergence of PML in natalizumab-treated patients—new cases, same concerns. N Engl J Med 2009;361:1041-3.
55. Aschermann Z, Gomori E, Kovacs GG, Pal E, Simon G, Komoly S, et al. X-linked hyper-IgM syndrome associated with a rapid course of progressive multifocal leukoencephalopathy. Arch Neurol 2007;64:273-6.
56. Carrasco R, Smith JA, Lovell D. Biologic agents for the treatment of juvenile rheumatoid arthritis: current status. Paediatr Drugs 2004;6:137-46.
57. Ruperto N, Lovell DJ, Cuttica R, Wilkinson N, Woo P, Espada G, et al. A randomized, placebo-controlled trial of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis. Arthritis Rheum 2007;56: 3096-106.
58. Young JD, McGwire BS. Infliximab and reactivation of cerebral toxoplasmosis. N Engl J Med 2005;353:1530-1.
59. Bustamante J, Boisson-Dupuis S, Jouanguy E, Picard C, Puel A, Abel L, et al. Novel primary immunodeficiencies revealed by the investigation of paediatric infectious diseases. Curr Opin Immunol 2008;20:39-48.
60. Wallis RS. Infectious complications of tumor necrosis factor blockade. Curr Opin Infect Dis 2009;22:403-9.
61. Kindler V, Sappino AP, Grau GE, Piguet PF, Vassalli P. The inducing role of tumor necrosis factor in the development of bactericidal granulomas during BCG infection. Cell 1989;56:731-40.
62. Zhang SY, Boisson-Dupuis S, Chapgier A, Yang K, Bustamante J, Puel A, et al. Inborn errors of interferon (IFN)-mediated immunity in humans: insights into the respective roles of IFN-alpha/beta, IFN-gamma, and IFN-lambda in host defense. Immunol Rev 2008;226:29-40.
63. Vogt G, Bustamante J, Chapgier A, Feinberg J, Boisson Dupuis S, Picard C, et al. Complementation of a pathogenic IFNGR2 misfolding mutation with modifiers of N-glycosylation. J Exp Med 2008;205:1729-37.
64. Lachmann HJ, Kone-Paut I, Kuemmerle-Deschner JB, Leslie KS, Hachulla E, Quartier P, et al. Use of canakinumab in the cryopyrin-associated periodic syndrome. N Engl J Med 2009;360:2416-25.
65. Mertens M, Singh JA. Anakinra for rheumatoid arthritis: a systematic review. J Rheumatol 2009;36:1118-25.
66. Picard C, von Bernuth H, Ghandil P, Chrabieh M, Levy O, Arkwright PD, et al. Clinical features and outcome of patients with IRAK-4 and MyD88 deficiencies. Medicine. In press. 2010.
67. von Bernuth H, Picard C, Jin Z, Pankla R, Xiao H, Ku CL, et al. Pyogenic bacterial infections in humans with MyD88 deficiency. Science 2008;321:691-6.
68. Salliot C, Dougados M, Gossec L. Risk of serious infections during rituximab, abatacept and anakinra treatments for rheumatoid arthritis: meta-analyses of randomised placebo-controlled trials. Ann Rheum Dis 2009;68:25-32.
69. Kishimoto T. Interleukin-6: from basic science to medicine—40 years in immunology. Annu Rev Immunol 2005;23:1-21.
70. Oldfield V, Dhillon S, Plosker GL. Tocilizumab: a review of its use in the management of rheumatoid arthritis. Drugs 2009;69:609-32.
71. Puel A, Picard C, Lorrot M, Pons C, Chrabieh M, Lorenzo L, et al. Recurrent staphylococcal cellulitis and subcutaneous abscesses in a child with autoantibodies against IL-6. J Immunol 2008;180:647-54.
72. Banchereau J, Pascual V. Type I interferon in systemic lupus erythematosus and other autoimmune diseases. Immunity 2006;25:383-92.
73. Yao Y, Richman L, Higgs BW, Morehouse CA, de los Reyes M, Brohawn P, et al. Neutralization of interferon-alpha/beta-inducible genes and downstream effect in a phase I trial of an anti-interferon-alpha monoclonal antibody in systemic lupus erythematosus. Arthritis Rheum 2009;60:1785-96.
74. Dupuis S, Jouanguy E, Al-Hajjar S, Fieschi C, Al-Mohsen IZ, Al-Jumaah S, et al. Impaired response to interferon-alpha/beta and lethal viral disease in human STAT1 deficiency. Nat Genet 2003;33:388-91.
75. Chapgier A, Kong XF, Boisson-Dupuis S, Jouanguy E, Averbuch D, Feinberg J, et al. A partial form of recessive STAT1 deficiency in humans. J Clin Invest 2009;119:1502-14.
76. Casrouge A, Zhang SY, Eidenschenk C, Jouanguy E, Puel A, Yang K, et al. Herpes simplex virus encephalitis in human UNC-93B deficiency. Science 2006;314:308-12.
77. Zhang SY, Jouanguy E, Ugolini S, Smahi A, Elain G, Romero P, et al. TLR3 deficiency in patients with herpes simplex encephalitis. Science 2007;317:1522-7.
78. Brinkmann MM, Spooner E, Hoebe K, Beutler B, Ploegh HL, Kim YM. The interaction between the ER membrane protein UNC93B and TLR3, 7, and 9 is crucial for TLR signaling. J Cell Biol 2007;177:265-75.
79. Reinisch W, de Villiers W, Bene L, Simon L, Rácz I, Katz S, et al. Fontolizumab in moderate to severe Crohn's disease: a phase 2, randomized, double-blind, placebo-controlled, multiple-dose study. Inflamm Bowel Dis 2010;16:233-42.
80. O'Neill JL, Kalb RE. Ustekinumab in the therapy of chronic plaque psoriasis. Biologics 2009;3:159-68.
81. Picard C, Fieschi C, Altare F, Al-Jumaah S, Al-Hajjar S, Feinberg J, et al. Inherited interleukin-12 deficiency: IL12B genotype and clinical phenotype of 13 patients from six kindreds. Am J Hum Genet 2002;70:336-48.
82. Altare F, Lammas D, Revy P, Jouanguy E, Döffinger R, Lamhamedi S, et al. Inherited interleukin 12 deficiency in a child with bacille Calmette-Guérin and *Salmonella enteritidis* disseminated infection. J Clin Invest 1998;102:2035-40.
83. Cárdenes M, Angel-Moreno A, Fieschi C, Sologuren I, Colino E, Molinés A, et al. Oesophageal squamous cell carcinoma in a young adult with IL-12Rβ1 deficiency. J Med Genet 2010;47:635-7.
84. Toyoda H, Ido M, Nakanishi K, Nakano T, Kamiya H, Matsumine A, et al. Multiple cutaneous squamous cell carcinomas in a patient with IFN-γ receptor 2 deficiency. J Med Genet 2010;47:631-4.
85. Li X. IRAK4 in TLR/IL-1R signaling: possible clinical applications. Eur J Immunol 2008;38:614-8.
86. Wang Z, Wesche H, Stevens T, Walker N, Yeh WC. IRAK-4 inhibitors for inflammation. Curr Top Med Chem 2009;9:724-37.
87. Maródi L, Notarangelo LD. Education and worldwide collaboration pays off. Nat Immunol 2007;8:323-4.
88. Maródi L, Casanova JL. Primary immunodeficiencies: the J Project. Lancet 2009; 373:2179-81.
89. Tóth B, Volokha A, Mihas A, Pac M, Bernatowska E, Kondratenko I, et al. Genetic and demographic features of X-linked agammaglobulinemia in Eastern and Central Europe: a cohort study. Mol Immunol 2009;46:2140-6.